Results of a Phase 2 Efficacy and Safety Study with SB204, an Investigational Topical Nitric Oxide–releasing Drug for the Treatment of Acne Vulgaris

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ABSTRACT

Objective: To compare efficacy, tolerability, and safety of two concentrations of topical SB204 and vehicle twice daily for 12 weeks in the treatment of acne vulgaris. **Design:** Randomized, double-blind, placebo-controlled, three-arm, Phase 2 study. **Setting:** Dominican Republic, Panama, and Honduras. **Participants:** Subjects with acne, age 12 to 40, with 25 to 70 noninflammatory lesions, 20 to 40 inflammatory lesions, and a baseline Investigator's Global Assessment score of mild, moderate, or severe. **Measurements:** The primary efficacy assessment was the absolute change in noninflammatory lesion counts. Other assessments included inflammatory lesion counts, success on dichotomized Investigator's Global Assessment, reported adverse events, physical examinations, laboratory testing, and tolerability. **Results:** One hundred fifty-three subjects were randomized to vehicle (n=52), SB204 1% (n=51), or SB204 4% (n=50). When compared to vehicle, subjects treated with SB204 1% and SB204 4% had significantly greater mean percent reduction in noninflammatory lesions from baseline and subjects treated with SB204 4% had a significantly greater mean percent reduction in inflammatory lesion count from baseline at Week 12. There were no significant differences in the IGA success rates between groups. Both concentrations of SB204 were safe and well-tolerated. **Conclusions:** When compared to vehicle, both SB204 1% and SB204 4% significantly decreased the percentage of noninflammatory lesions and SB204 4% also significantly decreased the percentage of inflammatory lesions in subjects with acne vulgaris treated for 12 weeks. Treatment with SB204 1% and SB204 4% was safe and well-tolerated. **Registry:** clinicaltrials.gov (NCT01844752). (*J Clin Aesthet Dermatol.* 2016;9(8):12–18.)

Acne vulgaris is a chronic, inflammatory skin disease in which inflammation induced by *Propionibacterium acnes* initiates and contributes to lesion formation.[1] The inflammatory cascade includes binding of *P. acnes* to the Toll-like receptor-2 (TLR-2) followed by activation of NLRP3 inflammasomes and caspase-1, which leads to secretion of pro-inflammatory cytokines.[2–4] These pro-inflammatory cytokines, including interleuken (IL)-1β, drive T cell differentiation and recruit lymphocytes and neutrophils to the acne lesion.[5] Activation of TLR2, which is expressed in basal and infundibular keratinocytes, also stimulates IL-1α release from keratinocytes.[6] TLR-2 activation and IL-1α secretion are postulated to be early steps in comedogenesis as IL-1α stimulates keratinocyte proliferation.

Nitric oxide, an endogenous rapid-acting gas, has both immunoregulatory and antimicrobial activity.[7,8] Importantly, nitric oxide has been shown to inhibit specific

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immunoregulatory pathways important in the pathogenesis of acne, particularly the NLRP3 inflammasome and caspase.[9,10] Recently, Qin et al [11] using a nitric oxide-based nanoparticle delivery system demonstrated that nitric oxide inhibited *P. acnes* growth and inhibited cytokine release from a *P. acnes* challenged human keratinocyte cell line and peripheral blood mononuclear cells.[11]

Nitric oxide targets bacteria through multiple nitrosative and oxidative mechanisms, leading to a low propensity for the development of resistance.[8,12,13] The innate antimicrobial and immunomodulatory activities of nitric oxide suggest nitric oxide may be an attractive candidate for the treatment of acne, particularly given the low risk for antimicrobial resistance.

To date, the development of topical nitric oxide treatments has been limited by the inability to store and safely deliver nitric oxide to the site of infection or inflammation. SB204 is a topical gel containing NVN1000, a nitric oxide-releasing macromolecule comprising a polysiloxane backbone with covalently bound N diazeniumdiolate nitric oxide donors.[14] NVN1000 has been formulated in an alcoholic gel and is co-administered with hydrogel to enhance nitric oxide release from the macromolecule at the time of SB204 application. Over 70 non-clinical studies have been completed to support the SB204 development program, including toxicology studies in rats, mice, and pigs for up to 39 weeks of topical treatment, with no significant safety findings (Novan, data on file). In pharmacokinetic studies in subjects with moderate-to-severe acne, topical administration of SB204 8% twice daily to 17 percent of body surface area was well-tolerated and demonstrated no detectable systemic exposure to the parent compound or nitric oxide metabolites using validated assays for the NVN1000 backbone and nitrate.[15,16]

The aim of this study was to compare the efficacy, safety, and tolerability of two concentrations (1% and 4%) of SB204 to vehicle applied twice daily to the face of subjects with acne vulgaris for 12 weeks.

METHODS

Study design. This study was a Phase 2, multicenter, randomized, double-blind, vehicle-controlled, parallel-group, three-arm study. The study protocol and amendments, informed consent forms, and other relevant documents were reviewed by local ethics committees and regulatory agencies in accordance with the requirements of each country prior to the start of the study.

Study subjects. Subjects were screened and enrolled from May 1, 2013, to August 14, 2013, at four dermatology clinical research sites in Latin America, including Dominican Republic, Panama, and Honduras. All subjects or their legal representative gave written informed consent prior to any study-related procedure. To be eligible for the study, subjects must have been between the ages of 12 and 40, must have been in good general health, and must have been diagnosed with acne vulgaris. Subjects were to have had 20 to 40 inflammatory lesions (papules and pustules), 25 to 70 noninflammatory lesions (open and closed comedones), ≤2 nodules on the face, and have a baseline Investigator's Global Assessment (IGA) score of 2 (mild), 3 (moderate), or 4 (severe). Female subjects of childbearing potential must have had a negative urine pregnancy test prior to randomization and must have agreed to use an effective method of birth control during the course of the study.

Subjects were excluded from the study if they had any dermatological condition or underlying disease on the face that could have interfered with clinical evaluations, required the use of topical or systemic therapy, or that might have made evaluation and lesion count inconclusive. Additional exclusion criteria included the initiation or discontinuation of estrogens less than 90 days prior to baseline evaluation, use of medications or vitamins known to exacerbate acne in the 180 days prior to baseline evaluation, or a history of hypersensitivity or allergic reaction to any ingredient in the study drug. The use of topical or systemic acne therapy was not permitted. Nitroglycerin, other nitric oxide donor drugs, or drugs associated with methemoglobinemia were also excluded as systemic exposure to nitric oxide leads to conversion of hemoglobin to methemoglobin. Subjects with a methemoglobin value of greater than two percent or clinically significant anemia at baseline were excluded from the study. The use of a long term (>10 day) course of antibiotics, systemic acne treatment, or corticosteroids (not including intranasal or inhaled preparations) within four weeks of baseline, systemic retinoids or vitamin A supplements (>10,000IU/day) within six months of baseline, or dermatological procedures or surgery within four weeks of baseline were causes for exclusion. Subjects could not have used additional investigational drugs or been enrolled in additional studies within 30 days of baseline and could not have participated in another study using NVN1000.

Treatment. Subjects were randomized to treatment with vehicle, SB204 1%, or SB204 4% in a 1:1:1 ratio. Subjects were instructed to apply topical gel evenly over the entire face twice daily, once in the morning and once at night after washing, for 12 weeks; each dose contained 900mg. Following the baseline visit, study visits took place every two weeks for the first four weeks, and every four weeks for the next eight weeks. If a subject terminated from the study, all assessments scheduled for Week 12 were to be conducted. The study duration was up to 12 weeks of treatment.

Efficacy assessments. The primary efficacy assessment was the absolute change in noninflammatory lesion count from baseline to Week 12. Additional efficacy assessments included percent change in noninflammatory lesions, absolute change in inflammatory lesion count, and percent change in inflammatory lesion count from baseline to Week 12. The change in dichotomized IGA scores at baseline and Week 12 was also assessed. The IGA score was determined based on investigator evaluation of the overall signs and symptoms of acne vulgaris and was scored on a scale of 0 (clear) to 4 (severe). Clinical photographs were collected at baseline, Week 4, and Week 12. All assessments were performed by investigators who were blinded to the subjects' treatment group assignment. For subjects who discontinued during the study, the last observation was

carried forward (LOCF) in the intent to treat (ITT) analysis.

Safety assessments. The number of applications of study treatment and subject compliance were evaluated. A subject was considered compliant with the dosing regimen if the subject applied at least 80 percent, but no more than 120 percent of the expected applications.

Safety assessments, including the incidence of adverse events (AEs), serious adverse events (SAEs), and AEs leading to study discontinuation, and changes in physical examination including blood pressure and pulse rate, were evaluated at the baseline, Week 2, Week 4, Week 8, and Week 12 visits. All reported AEs that occurred on or after the baseline date through the end of study were included in the analysis. Methemoglobin and hemoglobin were measured at the baseline, Week 2, and Week 12 visits using a Masimo Rainbow® SET® Rad-57™ pulse co-oximeter. Cutaneous tolerability assessments, including erythema, scaling, dryness, pruritus, and burning/stinging were evaluated by the investigator at the baseline, Week 2, Week 4, Week 8, and Week 12 visits and were graded on a scale of none, mild, moderate, or severe. At the baseline visit, cutaneous tolerability was assessed prior to application of treatment and 30 minutes following application of treatment. For all other visits cutaneous tolerability was assessed at least 30 minutes after treatment.

Statistical analysis. Approximately 150 subjects were to be randomized into the study in a 1:1:1 ratio at approximately four sites in Latin America. Assuming that the standard deviation of change in noninflammatory lesion count at Week 12 was approximately 20, a sample size of 50 subjects per treatment group had 80 percent power to detect an 11.4 point difference between any pair of treatments. Inferential statistics were intended to assist in characterizing the treatment and, thus, no adjustments were made for multiplicity.

Efficacy analyses were performed using the ITT population comprising all subjects who were randomized and dispensed study drug. Safety analyses were performed using the Safety Population comprising all randomized subjects with documented use of study drug (at least one application). Subjects who terminated early from the study had their last evaluation mapped to the most appropriate visit based on the midpoints between scheduled visits. The last observation was carried forward (LOCF) in order to provide a value for efficacy parameters that were missing, primarily due to missed visits.

The number of subjects enrolled, completed, and discontinued were summarized for each treatment group. Analysis of the least square (LS) absolute change and LS mean percent change in noninflammatory and inflammatory lesion count from baseline to Week 12 was conducted using an analysis of covariance (ANCOVA) with factors of treatment and investigational site and baseline lesion count as covariates. A linear regression was also performed to determine dose response where the slope (β) was estimated across treatments (SB204 1% and 4%) and where the vehicle was labeled as 0% for the regression. The null test was that $\beta = 0$ versus the alternative that β did not equal 0. Rejection of the null hypothesis with a positive β indicated a dose response.

Success in the dichotomized IGA score was defined as a score of "clear" (0) or "almost clear" (1) with at least 2-grade improvement from baseline. Clear was defined as skin with no inflammatory or noninflammatory lesions and almost clear was defined as skin with rare non-inflammatory lesions with no more than one inflammatory lesion. The primary analysis of the dichotomized IGA scores from baseline to Week 12 was performed using a logistic regression model where treatment and investigational sites were the independent factors. The dichotomized IGA score was relabeled as 0 for failure and 1 for success as the dependent variable in the logistic regression. Additionally, treatment groups were compared using the Cochran-Mantel-Haenszel (CMH) test stratified by investigational site. Pairwise comparisons were computed without concern for controlling for multiplicity.

All statistical processing was performed using SAS® version 9.3. Statistical significance was based on two-tailed tests of the null hypothesis resulting in p-values of ≤ 0.05.

RESULTS

Study population. A total of 153 subjects were randomized to the study; 52 subjects to the vehicle treatment group, 51 subjects to the SB204 1% treatment group, and 50 subjects to the SB204 4% treatment group (Figure 1). Twenty-four subjects did not complete the study due mostly to subject requests to withdraw (Figure 1).

Demographics and baseline characteristics were similar across all treatment groups in the ITT population (Table 1). The mean age of subjects was 19.8 years; 33.3 percent of subjects were 12 to 17 years of age, 60.1 percent of subjects were 18 to 29 years of age, and 6.5 percent of subjects were ≥30 years of age. The majority of subjects (99.3%) were Hispanic or Latino and 68.0 percent of subjects identified their race as "other." Mean lesion counts at baseline were similar across all treatment groups. The majority (79.1%) of all subjects had a baseline IGA score of "moderate."

Efficacy analysis. The primary endpoint for this study was the absolute change in noninflammatory lesion count from baseline to Week 12. The mean absolute change in noninflammatory lesion count from baseline to Week 12 in the ITT population was statistically significantly larger for the SB204 1% treatment group and the SB204 4% treatment group when compared to vehicle treatment ($p<0.05$). The mean absolute change in inflammatory lesion count from baseline to Week 12 was significantly larger for the SB204 4% treatment group ($p<0.05$) when compared to vehicle and demonstrated a linear dose response. The mean percent change in noninflammatory lesion count from baseline to Week 12 was significantly larger for both the SB204 1% and 4% treatment groups when compared to vehicle ($p<0.05$, Figure 2). The mean percent change in inflammatory lesion count from baseline to Week 12 was also statistically significantly larger for SB204 4%, when compared to vehicle (Figure 3). Changes in the noninflammatory and inflammatory lesion counts were evident as early as Week 4

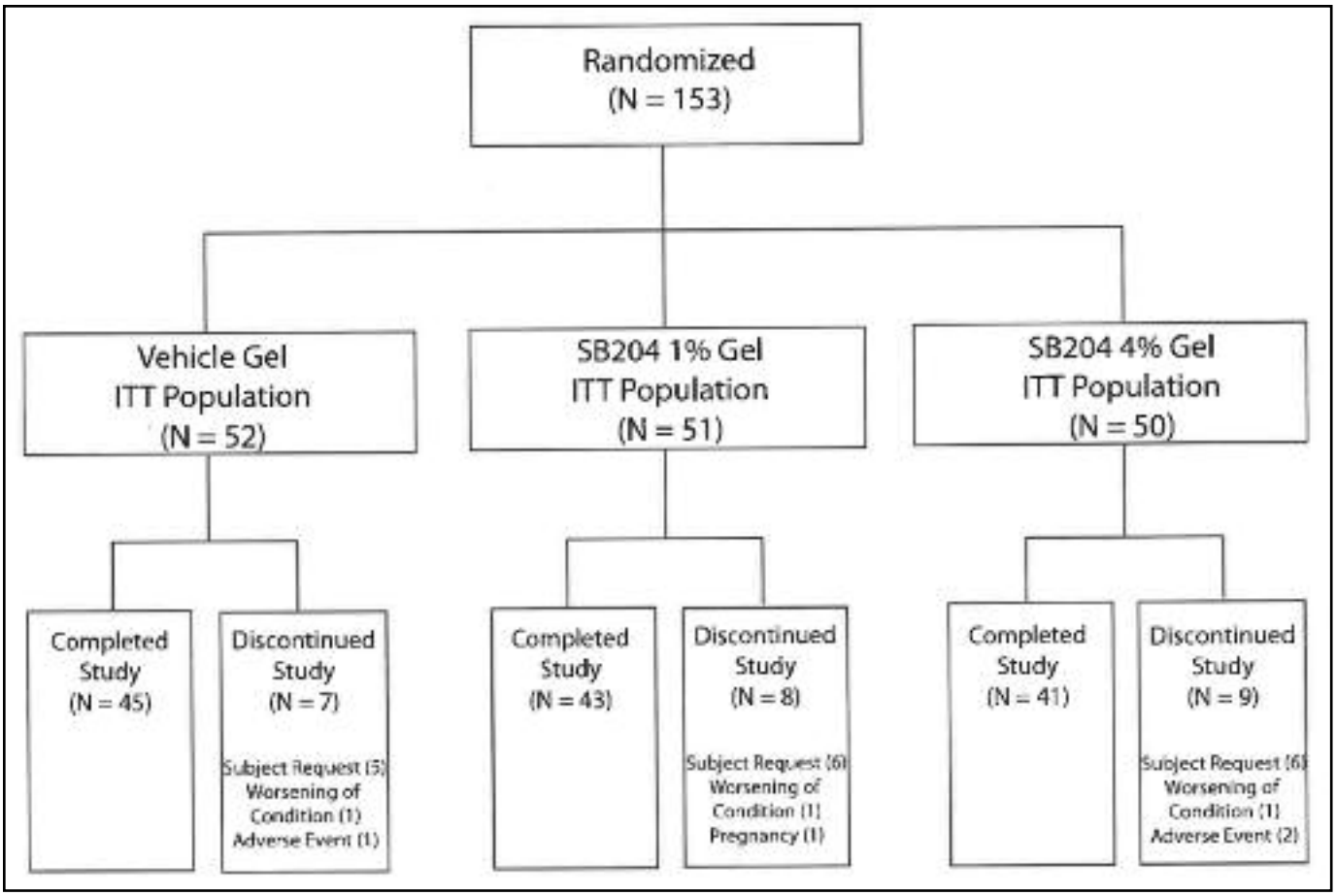

Figure 1. Subject disposition in the ITT population

for subjects treated with SB204 4%.

There were no significant differences in the dichotomized IGA scores between vehicle and SB204 1% or SB204 4% treatment groups. One subject (1.9%) in the vehicle treatment group, zero subjects in the SB204 1% treatment group, and one subject (2.0%) in the SB204 4% treatment group had success defined as IGA scores of "clear" or "almost clear" and at least a 2-grade improvement from baseline to Week 12. Clinical photographs from baseline and Week 12 for two subjects randomized to treatment with SB204 4% are shown in Figure 4.

Safety analysis. A total of 10 subjects (19.2%) in the vehicle treatment group and 20 subjects (19.8%) treated with SB204 reported at least one treatment-emergent AE (TEAE) over the course of the study (Table 2). Among subjects treated with SB204, the incidence of TEAEs was similar in the SB204 1% and SB204 4% treatment groups. The most frequent TEAEs observed in this study were headache (11 subjects), dysmenorrhea (10 subjects), and nasopharyngitis (6 subjects). Most TEAEs were mild in severity and were considered unrelated to study drug.

No SAEs occurred during this study. One subject was discontinued at Week 4 due to a pregnancy; the subject delivered a healthy infant after the study was completed. Three subjects (2 active, 1 vehicle) were discontinued from the study due to reported cutaneous AEs.

Overall, SB204 demonstrated good cutaneous tolerability at both concentrations. Tolerability scores at Week 12 in vehicle and SB204 treatment groups are displayed in Table 3. Among subjects with scores other than none on cutaneous tolerability assessments, most were mild in severity. Two subjects treated with SB204 4% were reported with severe burning/stinging as compared to zero subjects in the vehicle treatment group, while one subject treated with SB204 1% and two subjects treated with SB204 4% were reported to have severe pruritus, compared to one subject in the vehicle treatment group.

There were no clinically significant shifts in methemoglobin or total hemoglobin levels or changes in physical examination including vital signs.

DISCUSSION

The objective of this Phase 2 study was to determine the efficacy, safety, and tolerability of twice-daily topical SB204 at two concentrations in subjects with acne vulgaris treated for 12 weeks. SB204 1% and SB204 4% both significantly decreased the absolute lesion count and the percent change in lesion count of noninflammatory lesions when compared to vehicle over 12 weeks of treatment. SB204 4% significantly reduced the absolute lesion count and percent change in lesion count of inflammatory lesions when compared to vehicle. Treatment response was observed as early as four weeks after treatment initiation. While the precise mechanism of action of SB204 in reducing inflammatory and

TABLE 1. Demographics and baseline characteristics by treatment group (ITT population)

CHARACTERISTIC	VEHICLE (N = 52)	SB204 1% (N = 51)	SB204 4% (N = 50)	TOTAL (N = 153)
Mean age (SD)	20.0 (5.57)	20.0 (5.39)	19.3 (4.30)	19.8 (5.10)
Age group; n (%)				
Age 12–17	21 (40.4%)	16 (31.4%)	14 (28.0%)	51 (33.3%)
Age 18–29	27 (51.9%)	30 (58.8%)	35 (70.0%)	92 (60.1%)
Age ≥30	4 (7.7%)	5 (9.8%)	1 (2.0%)	10 (6.5%)
Sex; n (%)				
Male	25 (48.1%)	26 (51.0%)	26 (52.0%)	77 (50.3%)
Female	27 (51.9%)	25 (49.0%)	24 (48.0%)	76 (49.7%)
Race; n (%)				
Black/African American	15 (28.8%)	13 (25.5%)	12 (24.0%)	40 (26.1%)
White/Caucasian	2 (3.8%)	5 (9.8%)	2 (4.0%)	9 (5.9%)
Other	35 (67.3%)	33 (64.7%)	36 (72.0%)	104 (68.0%)
Mean noninflammatory lesion count, including nose (SD)	49.0 (14.12)	51.5 (13.27)	50.7 (14.67)	50.4 (13.98)
Mean inflammatory lesion count; mean (SD)	29.0 (5.98)	29.3 (5.87)	29.1 (5.11)	29.1 (5.64)
IGA Score; n (%)				
Mild severity	5 (9.6%)	3 (5.9%)	4 (8.0%)	12 (7.8%)
Moderate severity	36 (69.2%)	42 (82.4%)	43 (86.0%)	121 (79.1%)
Severe	11 (21.2%)	6 (11.8%)	3 (6.0%)	20 (13.1%)

IGA=Investigator's Global Assessment; SD=standard deviation

noninflammatory lesion counts in subjects with acne is unknown, topical administration of a nitric oxide-releasing compound may target both *P. acnes* and the innate immunoregulatory pathways relevant in acne vulgaris.[1–6]

This study demonstrated good cutaneous tolerability of SB204 in subjects with acne vulgaris. Observations of erythema, scaling, dryness, and reports of pruritus or stinging/burning were infrequent and when reported were generally mild in severity. No SAEs occurred during the study, and the majority of AEs were mild and unrelated to treatment with SB204. Three subjects discontinued from the trial due to AEs—two subjects treated with SB204 and one subject treated with vehicle.

In this study, subjects were treated and followed for 12 weeks; information about the safety and efficacy of SB204 with longer treatment or the durability of treatment response are unknown at this time.

These results demonstrated that twice-daily treatment with SB204 1% and 4% reduced noninflammatory and inflammatory lesion counts in subjects with acne vulgaris and had a rapid onset of clinical benefit. While the precise mechanism of action of SB204 in reducing inflammatory and noninflammatory lesion counts in subjects with acne is unknown, topical administration of a nitric oxide-releasing compound may target both *P. acnes* and the innate immunoregulatory pathways relevant in acne vulgaris. The results presented here demonstrating reduction in both inflammatory and noninflammatory lesion counts and a good

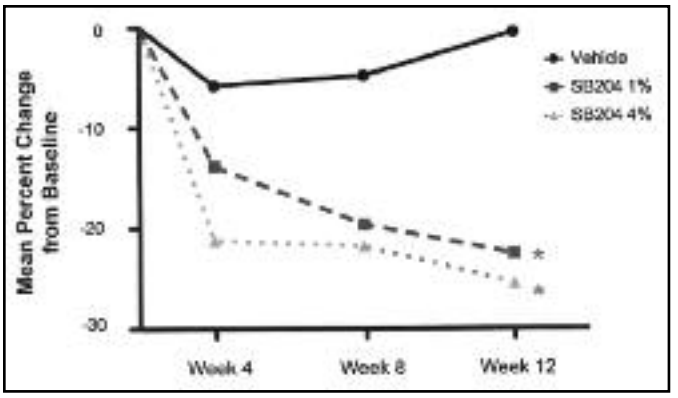

Figure 2. Mean percentage change: noninflammatory lesion count over time (ITT Population). *p<0.05

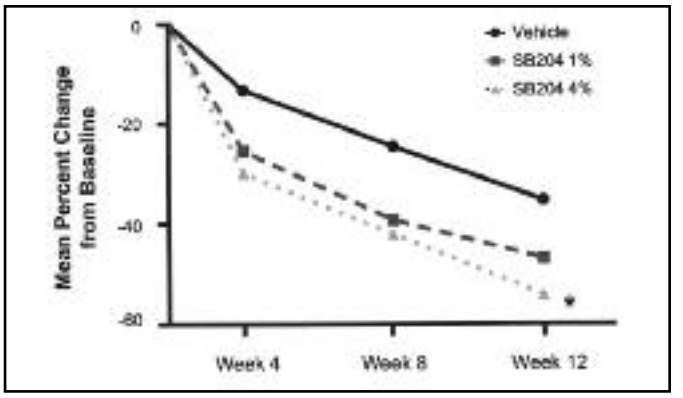

Figure 3. Mean percentage change: inflammatory lesion count over time (ITT Population). *p<0.05

tolerability and safety profile warrant additional studies with SB204 for the treatment of acne vulgaris.

CONCLUSION

When compared to vehicle, twice-daily application of SB204 1% and SB204 4% significantly decreased noninflammatory lesions in subjects with acne vulgaris treated for 12 weeks. Additionally, SB204 4% significantly decreased inflammatory lesions in subjects treated for 12 weeks. Treatment with SB204 1% and 4% was safe and well-tolerated.

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Figure 4. Photographs from Baseline and Week 12 from subjects randomized to SB204 4%

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TABLE 2. Summary of TEAEs by MedDRA System Organ Class and Preferred Term occurring at a frequency ≥5% in any treatment group (safety population)

SYSTEM ORGAN CLASS[a] PREFERRED TERM	VEHICLE (N = 52)	SB204 1% (N = 51)	SB204 4% (N = 50)	POOLED SB204 (N = 101)
Subjects reporting at least 1 TEAE; n (%)	10 (19.2%)	9 (17.6%)	11 (22.0%)	20 (19.8%)
Infections and infestations; n (%)	2 (3.8%)	4 (7.8%)	3 (6.0%)	7 (6.9%)
Nasopharyngitis	1 (1.9%)	3 (5.9%)	2 (4.0%)	5 (5.0%)
Nervous system disorders; n (%)	5 (9.6%)	1 (2.0%)	5 (10.0%)	6 (5.9%)
Headache	5 (9.6%)	1 (2.0%)	5 (10.0%)	6 (5.9%)
Reproductive system and breast disorders; n (%)	4 (7.7%)	3 (5.9%)	3 (6.0%)	6 (5.9%)
Dysmenorrhea	4 (7.7%)	3 (5.9%)	3 (6.0%)	6 (5.9%)

[a]Counts reflect numbers of subjects reporting one or more AEs that mapped to the MedDRA dictionary. At each level of summarization (System Organ Class or Preferred Term), subjects were only counted once
AE=adverse event; MedDRA=Medical Dictionary for Regulatory Affairs; TEAE=treatment-emergent adverse event
Treatment emergent adverse events were coded using MedDRA Version 16.0. Treatment emergent AEs were those with an onset after application of study medication

TABLE 3. Summary of cutaneous tolerability of SB204 by treatment group (safety population, Week 12)

	VEHICLE GEL (N = 45)			NVN1000 1% GEL (N = 43)			NVN1000 4% GEL (N = 41)		
	MILD	MODERATE	SEVERE	MILD	MODERATE	SEVERE	MILD	MODERATE	SEVERE
Erythema	4 (8.9%)	0 (0%)	0 (0%)	4 (9.3%)	2 (4.7%)	0 (0%)	6 (14.6%)	1 (2.4%)	0 (0%)
Scaling	1 (2.2%)	0 (0%)	0 (0%)	4 (9.3%)	0 (0%)	0 (0%)	8 (19.5%)	0 (0%)	0 (0%)
Dryness	4 (8.9%)	0 (0%)	0 (0%)	1 (2.3%)	0 (0%)	0 (0%)	5 (12.2%)	0 (0%)	0 (0%)
Itching	4 (8.9%)	0 (0%)	0 (0%)	3 (7.0%)	0 (0%)	0 (0%)	10 (24.4%)	0 (0%)	0 (0%)
Burning/stinging	3 (6.7%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	0 (0%)	3 (7.3%)	0 (0%)	0 (0%)

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